BASL Wilson's Disease Special Interest Group Meeting

Thursday 14th December 2017

Burroughs Room, Wellcome Collection, 183 Euston Road, London NW1 2BE

Attendee list: Please see Appendix A

Apologies received: Please see Appendix B

Meeting report

This was the inaugural BASL Wilson's SIG meeting. 30 attendees from the following centres participated: – Birmingham, Cambridge, Grampian, Kings, Newcastle, Queen Square (UCL), Royal Free/UCL, Royal Surrey (University of Guilford), Sheffield and Southampton. Attendees from these Centres represented a wide range of specialisation including Metabolic Medicine, Clinical Chemistry/Biochemistry, Molecular Genetics, Hepatology, Paediatric Hepatology and Neurology. In addition, representatives from Public Health England (based in Newcastle) and the UK Wilson's Disease Support Group contributed to the meeting. This was the first Wilson's SIG to have been sponsored by BASL, with the purpose of being democratic and inclusive, as well as demonstrating proof of function and value to the subject.

Meeting summary and action points:

A formal agenda was followed (see **Appendix C**).

Potential for recognized Specialist Centres and their function

- NHS Trientine Policy Update. Dr James Dooley (Royal Free/UCL): JD presented the background for the instigation of a Policy group (January 2016) which was predicated by an increase in cost of trientine dihydrochloride and the need for this medication to come 'off tariff'. An NHS policy was therefore required for its use. He presented the membership of the group and the progress to date. One draft policy had been produced after a NICE Evidence Review on trientine dihydrochloride, but the clinical panel had not accepted this as it stood, requiring more data on the use of zinc salts. This evidence review had been completed and a revised draft policy was in preparation for discussion by the Policy Group. It was anticipated that this

would be done in early 2018, presented to the Clinical Panel, and if approved would go through further groups before it could be adopted. As part of the previous draft document, the Policy Group had recommended (a) the setting up of a National Advisory Panel to monitor and advise on trientine use, and (b) the recognition of specialist centres in England, both for the progression of best practice in Wilson's Disease patients, and as a resource for the review of patients on an agreed basis/frequency. It was anticipated that there would be approximately 10 specialist units recognised in England, but this strategy was in development.

Action: JD to continue leading the working party and for the Policy Group to report back to the SIG in due course

- Lessons from NHS England Hepatology Operational Delivery Networks (ODNs) for the development of Wilson's Disease Centres (Prof Aftab Ala, Royal Surrey/University of Guildford): AA described the HCV and PBC 'hub and spoke' networks within Hepatology set up to deliver coordinated treatment via NHSE specialised commission. He described how 'Wilson's centres' might be envisaged with multi-disciplinary input.
- In discussion it was agreed that the currently established centres seeing cohorts of Wilson's patients could form the basis of a model of care within England. These encompass both paediatric and adult departments. It was agreed that whichever CRG submits a proposal for Wilson's Disease (hepatology/neurology/metabolic) via the rare disease advisory group (RDAG) to NHSE, it would be an all inclusive application. The HPB CRG is willing to accept a submission by mid-January 2018 with a view to NHSE commissioning of a 'highly specialised service' for Wilson's disease. This would comprise a small number of adult centres of excellence providing MDT clinics and pathways with a 'hub and spoke' arrangement with the smaller Trusts and having transition service links with the paediatric centres. Professor Deidre Kelly offered assistance with this application, and it was agreed that all interested in the SIG/WD community would have a part to play.

Action: BG/GA with input from other interested members of the group will submit a proposal via the HPB CRG. A list of potential adult and paediatric units with a specialist interest is attached (**Appendix D**).

National Data Collection

- WDSG UK patient registry - Jerry Tucker: JT reported that 54 patients are registered – 52 formal members of WDSG-UK and 2 Facebook members (from a total of 275 Facebook members, approx. 150 of whom are patients). Only contact information is stored but the WDSG are able to map out responders geographically across the UK.

- Public Health England Rare Disease project - Mary Bythell, Newcastle: MB outlined the strategy and potential approaches for their Wilson's Disease project. Based on existing NCARDRS work there is a national infrastructure for case registration of congenital anomalies, and data sharing arrangements with Trusts across England, through section 251 agreement. One consequence of this registration process is to be able to examine prevalence rates and epidemiology. 'Rare disease' is a completely new development within this structure and

Wilson's disease was chosen as a potential pilot focus after discussion with Prof Graeme Alexander (GA) at BASL.

The aim is to retrospectively identify cases of Wilson's Disease via a number of routes including data from Hospital Episode Statistics (HES), the Office for National Statistics (ONS), GP prescribing, genetic testing laboratories, NHS Blood and Transplant (NHSBT), and via mental health and primary care electronic systems. Primary care data systems may be more directly accessible in the future as they upgrade their coding software and this would potentially be a powerful approach in terms of capture. The SIG group also suggested accessing data from laboratories involved in analysing copper in serum and urine. There are limitations to each of these approaches in terms of data capture and diagnostic accuracy. For example HES is for inpatient and not outpatient diagnoses. Dr Richard Kirk pointed out that there will be consolidation of genetic laboratories nationally next year, which will result in probably 7 hubs, of which 2-4 would provide Wilson's gene testing.

The PHE project aims initially to store registry data (including WD patients who are alive, those who have died and those transplanted) within the NCARDRS database. In the future the data may be stored prospectively, and may ultimately be analysed using advanced rare disease statistics. The SIG members present were very keen to collaborate in this project with PHE. It was suggested that a subgroup from the membership could be formed for Wilson's epidemiological research in partnership with PHE.

Action: MB to ask SIG members for lists of patients in order to validate their methodologies. Where data sharing/transfer arrangements are not in place with specific Trusts, PHE would be able to advise on the process for doing this

Research

- Bis-choline TTM: Dr David Nicholl, Birmingham: DN outlined the phase 2 study published this year in Lancet Gastro/Hepatology. A Phase 3 study is in development with a study protocol being finalised imminently, hoping to recruit 100 cases worldwide with a target of approximately one quarter being treatment naive patients. There was discussion about the unmet need for neurological disease in terms of reliable and effective therapy. Whether stable asymptomatic patients would wish to change their treatment was discussed. The SIG agreed that a small number of patients across the centres might be suitable for enrolment.

Action: DN *to* circulate the study protocol to the SIG

- Aspects of chelator chemistry – Dr Bill Griffiths, Cambridge: BG summarised information from slides that Rupert Purchase (RP) had hoped to present but in the event RP was unable to attend to do so. Current agents have different modes of action and there is still much that is unknown about the mechanism of D-penicillamine and the effect of TTM on copper-containing proteins. Godfrey Gillett pointed out that ammonium TTM (the formulation of TTM used in the past) could be re-manufactured in the UK if there was a need.

Action: BG to ask RP to elaborate on the differences between chelators at the next SIG meeting. This would fit in well with other items on the proposed agenda including laboratory analysis, and diagnostics in more detail

- The Wilson's Disease registry / clinical database study across 5 centres in the US - Prof Aftab Ala, Royal Surrey: AA described this study, recent launched with funding from the US Wilson's Disease Association, which has several aims including to understand the natural history of Wilsons Disease, improve diagnostic testing, analyse treatment strategies, compare outcomes and evaluate monitoring aspects. The Chemical Pathology department in Guildford are funded to provide the copper diagnostics for this study. The current participants hope to enrol 300 patients and will invite centres from the UK and Europe to take part.

Action: AA to circulate further details to the SIG membership

- Biomarkers and genetics in neurological Wilson's - Dr Sam Shribman on behalf of Prof Tom Warner, Queen Square, UCL: SS presented the background and proposed study protocol for this new project. They will evaluate a panel of markers and their correlation with neurological involvement due to Wilson's Disease using MRI, plasma and CSF analysis. The aim of the protocol to try to find methodology by which to better assess and monitor neurological involvement. A second aim is to determine which patients are at increased risk of neurological disease and deterioration. This will involve genetic studies including GWAS. Local funding is in place at present for this project.

Action: SS/TW to access Wilson's cohorts with help of the SIG

- Drug-screening models – Prof Oliver Bandmann, Sheffield: OB described a skin fibroblast model for high throughput drug screening protocols which can be performed independently from Pharmaceutical Companies, based on biopsy material from patients with neurological disease and mitochondrial dysfunction. Neural progenitor cells (i-neurons) can be differentiated from skin fibroblasts using an iPSC method. This provides a potential model for drug screening. OB also described an ATP7B knock out Zebrafish. This model develops oxidative stress which can be imaged and provides a model for advancing understanding of Wilson's disease. The opportunity for collaboration with SS/TW was raised in providing skin samples from patients with Wilson's disease for study.

Concluding discussion

1. There was discussion with regard to SIG group's involvement with the pharmaceutical industry. It was concluded that the SIG should see itself as the interface for Pharma wishing to explore therapeutic trials in Wilson's disease in the UK.
2. At the next meeting the SIG was keen to have a presentation on novel therapeutic avenues such as gene editing / RNA interference. The SIG members agreed that an academic and/or specific company working on this area could be invited to give a presentation. They did not consider that this would represent a conflict of interest for the group.

3. BASL could survey which of its members care for patients with Wilson's Disease. Additionally, BASL could instigate a national audit by gastro/liver SpRs within Trusts to facilitate data collection for Wilson's Disease.
4. BASL will seek nominations and elect a formal Chair for this Wilson's Disease Special Interest Group. Such nominations would not be confined to those within Hepatology. BASL would also circulate information through other relevant societies and welcome other interested members via these routes. Suggestions for such wider membership would involve liaison between BASL and the existing SIG members.
5. Date of next meeting – to be decided but this is expected to be in approximately 6 months. A London venue appeared to be preferable to the group in terms of ease of access.
6. Depending on numbers attending, BASL may need to seek additional funding.
7. It was suggested that the agenda for the next meeting would include matters arising from the December meeting, but also a) laboratory assay/diagnostics; b) copper chemistry and TTM formulations, and c) updates on projects with novel research avenues.

BG/JD 14.1.18